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Interactive report

Basal ganglia and cerebellar loops: motor and cognitive circuits [1]

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Abstract

The traditional view that the basal ganglia and cerebellum are simply involved in the control of movement has been challenged in recent years. One of the pivotal reasons for this reappraisal has been new information about basal ganglia and cerebellar connections with the cerebral cortex. In essence, recent anatomical studies have revealed that these connections are organized into discrete circuits or 'loops'. Rather than serving as a means for widespread cortical areas to gain access to the motor system, these loops reciprocally interconnect a large and diverse set of cerebral cortical areas with the basal ganglia and cerebellum. The properties of neurons within the basal ganglia or cerebellar components of these circuits resembles the properties of neurons within the cortical areas subserved by these loops. For example, neuronal activity within basal ganglia and cerebellar loops with motor areas of the cerebral cortex is highly correlated with parameters of movement, while neuronal activity within basal ganglia and cerebellar loops with areas of the prefrontal cortex is more related to aspects of cognitive function. Thus, individual loops appear to be involved in distinct behavioral functions. Studies of basal ganglia and cerebellar pathology support this conclusion. Damage to the basal ganglia or cerebellar components of circuits with motor areas of cortex leads to motor symptoms, whereas damage of the subcortical components of circuits with non-motor areas of cortex causes higher-order deficits. In this report, we review some of the new anatomical, physiological and behavioral findings that have contributed to a reappraisal of function concerning the basal ganglia and cerebellar loops with the cerebral cortex.

Keywords: Virus tracing; Primate; Prefrontal cortex; Globus pallidus; Substantia nigra; Dentate nucleus

Contents

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1. Introduction

The basal ganglia and cerebellum are two groups of subcortical nuclei that have classically been regarded as motor structures. Damage to these brain regions produces well-described alterations in motor function such as tremor, rigidity, akinesia or dysmetria (reviewed in [16,19,32,63]). Many of these symptoms are thought to be due to disruption of basal ganglia or cerebellar outputs to areas of the cerebral cortex involved in the control of movement. In fact, for many years, it was believed that the only areas of the cerebral cortex that were the target of basal ganglia and cerebellar output were those that participated in the generation and control of movement. Information that the basal ganglia and cerebellum received from other cortical areas in the prefrontal, parietal and temporal lobes was thought to be integrated in these subcortical nuclei and converted into commands for directing motor output at the level of the primary motor cortex (M1) [3,4,10,40,80]. Thus, basal ganglia and cerebellar loops with the cerebral cortex were seen as a mechanism for 'funneling' information into the motor system.

Over the past 10–15 years, an accumulation of information about the basal ganglia and cerebellum has led many investigators to challenge the funneling hypothesis. In 1986, Alexander, DeLong and Strick [2] theorized that the output of the basal ganglia targeted not only the primary motor cortex, but also specific areas of premotor and prefrontal cortex. These areas included an oculomotor area of cortex (the frontal eye field), and three regions of the prefrontal cortex (the dorsolateral prefrontal cortex, lateral orbitofrontal cortex, and anterior cingulate/medial orbitofrontal cortices). As a consequence, the basal ganglia were thought to have the ability to influence not only motor control, but also several different types of cognitive and limbic functions. In much the same manner, Leiner, Leiner and Dow [87–91] hypothesized that the output from the lateral deep cerebellar nucleus (the dentate) influenced not only motor areas of the cerebral cortex, but also areas of the prefrontal cortex involved in language and cognitive function.

Until recently, it has been difficult to evaluate the validity of these and other proposals because of the technical difficulty in reliably tracing multi-synaptic circuits that comprise basal ganglia and cerebellar loops. Hence, there has been considerable uncertainty about the cortical targets of basal ganglia and cerebellar output (but see [69,108, 117,132,135,136,169,174]). We have developed a new technique for tracing circuits in the central nervous system of primates, retrograde transneuronal transport of herpes simplex virus type 1 (HSV1). This technique makes it possible to determine the cortical targets of basal ganglia and cerebellar output [150,177]. When specific strains of HSV1 are injected into the cerebral cortex, the virus is taken up and transported in the retrograde direction to label the cell bodies of neurons that innervate the injection site. For example, two to three days after cortical injections of the McIntyre-B strain of HSV1 labeled neurons are found in the ventrolateral nucleus of the thalamus. After five days, virus is transported transneuronally in the retrograde direction and labels neurons at subcortical sites that project to the ventrolateral thalamus (i.e., output nuclei in the basal ganglia and cerebellum). Thus, this technique enables one to map basal ganglia-thalamocortical and cerebello-thalamocortical pathways in primates [65,66,94,98–104,160,153–159,152,177].

Results using this approach clearly indicate that the basal ganglia and cerebellum do not funnel information from widespread cortical areas to the primary motor cortex. Rather, these subcortical nuclei appear to project to many or most of the same cortical areas that send efferents to them. These observations raise the possibility that multiple closed-loop circuits form the anatomical substrate for basal ganglia and cerebellar interactions with the cerebral cortex. Surprisingly, the targets of basal ganglia and cerebellar output include not only regions of frontal and prefrontal cortex, but also specific areas of inferotemporal and posterior parietal cortex ([99]; West, Lynch and Strick, unpublished observations). The projections to these different cortical areas appear to arise from distinct regions of the output nuclei of the basal ganglia and cerebellum. In previous reports, we have suggested that the clustering of neurons within an output nucleus that projects to a given cortical area via the thalamus forms a distinct 'output channel' [65,66,94,98–104,160,153–159,152,177]. In this paper, we review these anatomical findings and also present some of the evidence that indicates individual output channels are concerned with different aspects of behavior. Finally, several of the neurologic and psychiatric implications of these observations will be discussed, particularly with regard to how the anatomical framework we have described may help explain some of the cardinal symptoms of schizophrenia.

2. New anatomical findings — multiple cortical areas are the target of basal ganglia and cerebellar output

2.1. Primary motor cortex

The initial series of experiments that used HSV1 as a transneuronal tracer examined the organization of basal

ganglia and cerebellar outputs to M1. Five days after injections of HSV1 into the arm area of M1 (Fig. 1), many 'second-order' neurons were labeled in output nuclei of the cerebellum (dentate and interpositus) and the basal ganglia (the internal segment of the globus pallidus [GPi]) [65,66,177].

In the cerebellum, labeled neurons in interpositus were largely confined to caudal portions of the anterior division of the nucleus, and those in the dentate were restricted to dorsal portions of the nucleus at mid rostro-caudal levels (Fig. 2, 'M1 arm'). These regions of the dentate and interpositus correspond to the sites in these nuclei where neurons related to arm movements have been recorded in electrophysiological studies [10,111,129,159,162,168].

In GPi, neurons labeled by the M1 injections were confined to the middle of the nucleus rostro-caudally, and formed two distinct clusters in the outer and inner portions of GPi (Fig. 3, 'M1 arm'). This region of GPi corresponds to the site where neurons related to arm movements have been recorded in electrophysiological studies [6,31–33, 55,105,176].

These results confirm that the arm area of M1 is the target of output from both the basal ganglia and the cerebellum. Furthermore, these observations indicate that the projections from the dentate, interpositus and GPi to the arm area of M1 (via the ventrolateral thalamus) originate from a specific region within each subcortical structure. In other experiments, injections of HSV1 into the face and leg areas of M1 demonstrated that the dentate, interpositus and GPi each contained a body map that projected to M1 in a somatotopically organized fashion [66]. Furthermore, these experiments indicated that a relatively small volume of these three subcortical nuclei is devoted to M1 output.

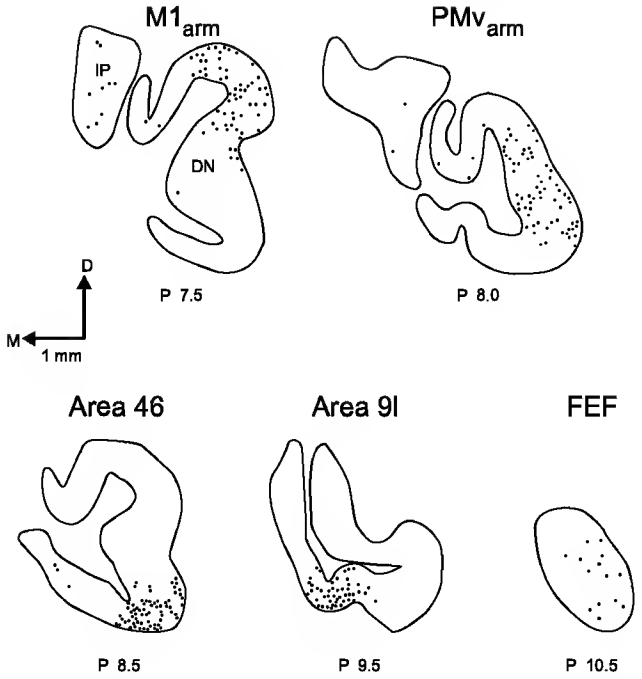

Fig. 2. Dentate projections to motor and non-motor cortical areas. Injections of HSV1 into portions of M1, PMv, area 46, area 9 and the FEF all labeled neurons in different regions of the dentate nucleus. Representative coronal sections through the dentate of animals that received these injections are shown. The sections display labeled neurons found on 1–3 adjacent sections. Adapted from [103].

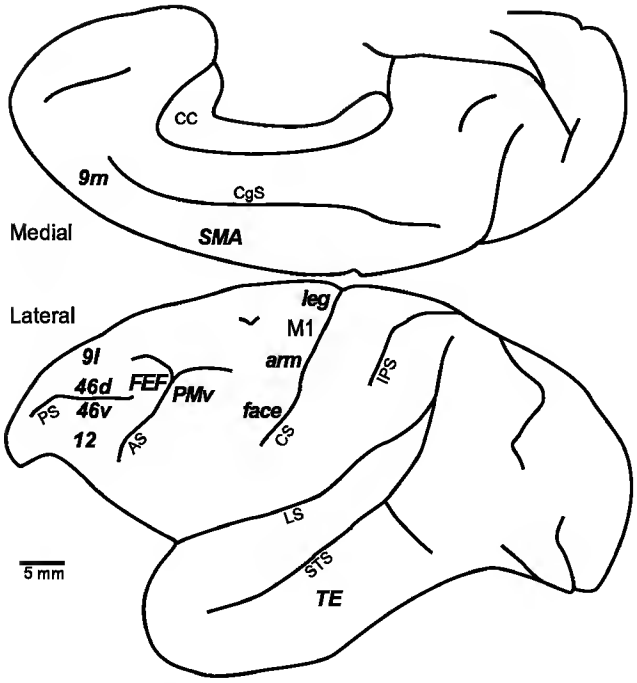

Fig. 1. Cortical targets of basal ganglia and cerebellar output. Areas labeled in bold represent cortical regions that were injected with the McIntyre-B strain of HSV1. Retrograde transneuronal transport of the virus labeled neurons in GPi, SNpr or the dentate nucleus of the cerebellum. AS, arcuate sulcus; CC, corpus callosum; CgS, cingulate sulcus; CS, central sulcus; FEF, frontal eye field; IPS, intraparietal sulcus; LS, lateral sulcus; M1, primary motor cortex; PMv, ventral premotor area; PS, principal sulcus; SMA, supplementary motor area; STS, superior temporal sulcus; TE, area of inferotemporal cortex. Adapted from [104].

2.2. Premotor cortex

We next examined basal ganglia and cerebellar outputs to the arm representations of two premotor areas in the frontal lobe, the ventral premotor area (PMv) and the supplementary motor area (SMA) (Fig. 1) [65,152]. Injections of HSV1 into the PMv labeled neurons in the middle of the dentate rostro-caudally (Fig. 2, 'PMv arm'). Moreover, these labeled neurons were located ventral and lateral to the region of the dentate that contained labeled neurons after virus injections into the arm area of M1 (compare Fig. 2, 'M1 arm' and 'PMv arm'). Thus, the arm areas in M1 and PMv receive input from different portions of the dentate. This organization creates at least two distinct 'output channels' in the sensorimotor portion of the dentate [152].

In GPi, virus injections into either the PMv or SMA consistently labeled neurons in the middle of the nucleus rostro-caudally. Within this region, the dorsoventral loca-

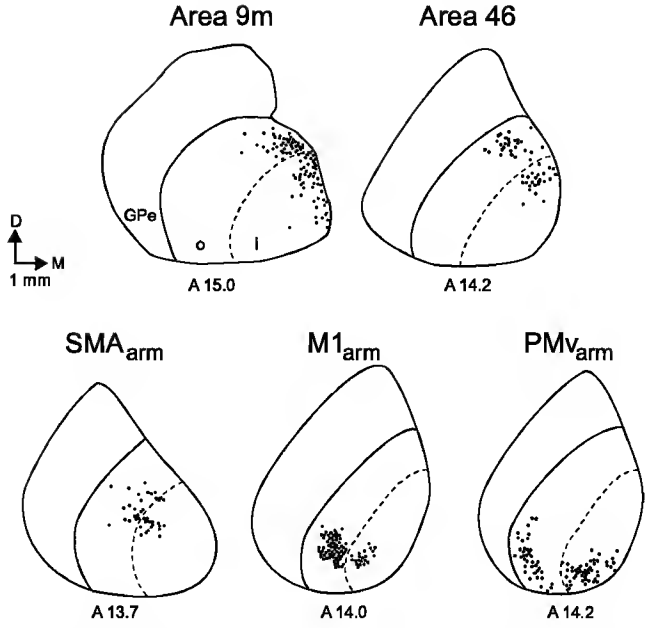

Fig. 3. Pallidal projections to motor and non-motor cortical areas. Injections of HSV1 into portions of M1, PMv, SMA, and areas 46 and 9 all labeled neurons in GPi. The conventions for this figure are the same as those for Fig. 2. GPe, external segment of globus pallidus; o, outer portion of the internal segment of globus pallidus; i, inner portion of the internal segment of globus pallidus. Adapted from [104].

tion of labeled neurons varied depending on the location of the cortical injection site. The SMA injections labeled neurons in a mid-dorsal region of GPi (Fig. 3, 'SMA arm'). In contrast, PMv injections labeled neurons mainly in ventrolateral portions of GPi (Fig. 3, 'PMv arm'). Neurons labeled by virus injections into M1 were located between those labeled by the SMA and PMv injections (Fig. 3). These observations lead to two important conclusions. First, pallido-thalamocortical projections target premotor, as well as primary motor areas of the cerebral cortex. Second, the arm representation of each motor area receives input from a topographically distinct set of GPi neurons. Thus, at least three distinct output channels are present in the sensorimotor portion of GPi [65].

2.3. The frontal eye field

In another set of experiments, we examined subcortical inputs to the frontal eye field (FEF) located in Walker's area 8 [94,165]. This cortical region has long been recognized as an important component of the cortical system that controls voluntary eye movements in primates (see [20]). Injections of virus were made into a portion of the FEF where intracortical stimulation evoked saccades (Fig. 1). Second-order neurons labeled by retrograde transneuronal transport were found in the dentate nucleus of the cerebellum and the pars reticulata of the substantia nigra (SNpr), as the oculomotor layers of the superior colliculus.

Within the dentate, labeled neurons were found only in the most caudal third of the nucleus (Fig. 2, 'FEF'). Prior studies have shown that this region contains some neurons that display changes in activity correlated with saccadic eye movements [162]. Within the basal ganglia, FEF injections labeled neurons in a lateral region of SNpr (Fig. 4, 'FEF') and not in GPi. These labeled neurons were located mainly in the posterior two-thirds of the SNpr. Neurons in this region of the SNpr have been observed to display changes in activity related to saccadic eye movements [61,62]. The regions of the dentate and SNpr labeled after FEF injections were strikingly different from the regions of these nuclei that were labeled after injections into M1 or PMv (Figs. 2 and 4). Thus, the dentate and SNpr contain separate skeletomotor and oculomotor output channels.

2.4. Prefrontal cortex

As noted above, there have been a number of suggestions that the basal ganglia and cerebellum influence some of the cognitive operation normally thought to be subserved by the frontal lobe (e.g., [2,87–91]). We used transneuronal transport of HSV1 to test whether basal ganglia-thalamocortical and cerebellar-thalamocortical pathways to the frontal lobe form the anatomical basis for this influence [98,100–104]. Initially, we focused on cerebellar and basal ganglia projections to portions of Walker's areas 9, 12 and 46 (Fig. 1). Each of these areas appears to be involved in aspects of 'working memory' and is thought to guide behavior based on transiently stored information rather than immediate external cues (for in-depth review, see [47,52,126]).

Injections of HSV1 into areas 9 and 46 (but not area 12) labeled many neurons in the dentate nucleus. These labeled neurons were confined to the most ventral portions of the dentate and were concentrated rostro-caudally in the mid-

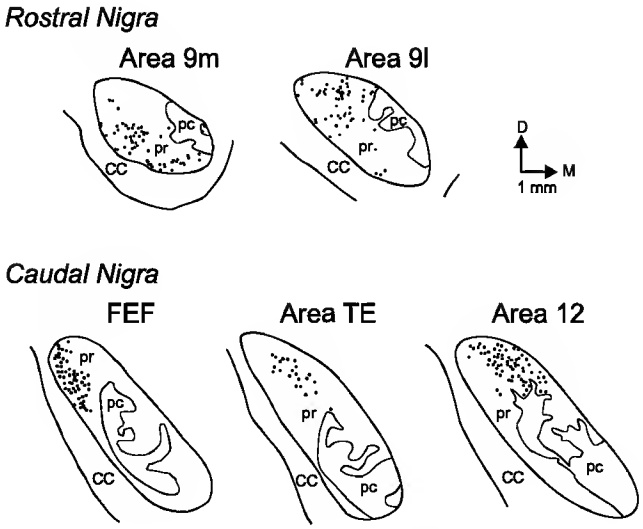

Fig. 4. Nigral projections to motor and non-motor cortical areas. Injections of HSV1 into portions of area 9, area 12, the FEF, and area TE all labeled neurons in SNpr. The conventions for this figure are the same as those for Fig. 2. CC, crus cerebri; pc, pars compacta; pr, pars reticulata. Adapted from [104].

dle third of the nucleus (Fig. 2, 'Area 46' and 'Area 9l'). The neurons labeled after area 9 injections were found largely medial to the neurons labeled by area 46 injections. The ventral regions of the dentate that project to areas 9 and 46 clearly differed from the more dorsal regions of this nucleus that innervate M1 or the PMv and the more caudal region of the dentate that innervates the FEF (Fig. 2).

In the basal ganglia, many neurons were labeled after virus injections into all three prefrontal areas. Injections into area 12 labeled neurons in the caudal and dorsomedial portion of SNpr, but not GPi (Fig. 4, 'Area 12'). In contrast, virus injections into area 46 labeled many neurons in dorsomedial portions of GPi (Fig. 3, 'Area 46') but relatively fewer neurons in SNpr (not illustrated). Injections into area 9 labeled many neurons in rostral portions of both GPi and SNpr (Figs. 3 and 4). In addition, the clustering of neurons within the GPi and SNpr that projected to each prefrontal area appeared to be topographically distinct, even when the projections were directed to two subdivisions of a single cortical area (Fig. 4, 'Area 9m' and 'Area 9l').

Overall, our observations on basal ganglia and cerebellar pathways to the prefrontal cortex suggest two important conclusions. First, multiple areas of prefrontal cortex are the target of output from distinct regions of the basal ganglia and/or cerebellum. Second, the output channels in the basal ganglia and cerebellum that influence prefrontal cortex are separate from those that influence the cortical motor areas [98,100–104].

2.5. Inferotemporal cortex

Each of the cortical regions that we have shown is a target of basal ganglia and/or cerebellar output also is known to project to these subcortical nuclei (reviewed in [2,103,151,177]). This anatomical arrangement suggests that many areas in the frontal lobe participate in 'closed' loops with the basal ganglia and cerebellum. We tested whether this arrangement extends to areas outside the frontal lobe by examining subcortical inputs to a region of inferotemporal cortex, area TE [99]. TE has well-described inputs to the basal ganglia [134], and is known to play a critical role in the visual recognition and discrimination of objects [54,107,157].

Injections of HSV1 into area TE led to a distinct cluster of labeled neurons in SNpr (Fig. 4 'Area TE'). Most of these neurons were located dorsally in the caudal third of the nucleus. This portion of the SNpr appears to be separate from the regions of this nucleus that influence either the FEF or regions of prefrontal cortex (Fig. 4). Thus, TE is both a source of input to, and target of output from, a distinct portion of the basal ganglia.

The region of SNpr that influences TE has been shown to contain some neurons that display changes in activity related to the presentation of visual stimuli [61,62]. This observation, together with our anatomical results, suggests that the basal ganglia may be involved in higher order aspects of visual processing, in addition to their involvement in motor and cognitive function. Many cortical areas other than the ones we have examined project to the basal ganglia and/or to the cerebellum. Whether all of these cortical areas are the target of basal ganglia or cerebellar output remains to be determined. Preliminary findings indicate, however, that specific regions of the posterior parietal cortex may participate in closed loop circuits with the basal ganglia and cerebellum (West, Lynch and Strick, unpublished observations). Thus, closed loop circuits may be a fundamental feature of basal ganglia and cerebellar interactions with the cerebral cortex.

3. Physiological studies

Our anatomical findings raised an important question regarding the function of output channels. Specifically, do individual output channels send similar or different types of information to the cortical areas they innervate? For example, do neurons in the dentate output channel that projects to area 46 have the same or different response properties as neurons in the output channel to M1? To begin to address this question, we recorded the activity of single neurons in both the dentate nucleus and the globus pallidus of monkeys during the performance of behavioral tasks that included motor and cognitive components [111–113].

3.1. Single neuron recording in the basal ganglia and cerebellum

Monkeys were trained to perform sequential pointing movements under two task conditions. In both conditions, the monkey faced a panel with five touch pads which were numbered 1 to 5 (left to right). A small red light emitting diode (LED) was located over each touch pad. The monkey began a trial by placing his right hand on a hold key in front of him for a variable 'Hold' period. In the Remembered Sequence Task (REM task), LEDs over three touch pads were illuminated in a sequence as an instruction to the monkey. At the end of a variable 'Instruction' period, an auditory 'Go' signal told the monkey to release the hold key and press the three touch pads according to the instructed sequence (i.e., in the same order that the LEDs were illuminated). Thus, the specific sequence of movements that the monkey performed during each trial of the REM task was initially stored in 'working memory' and then, internally cued.

In the Tracking Task (TRACK task), an LED over a single touch pad was illuminated after the 'Hold' period. The auditory 'Go' signal was turned on at the same time. Following the onset of this signal, the monkey was required to release the hold key and press the indicated touch

pad. As soon as the monkey contacted the first touch pad, a second LED over another touch pad was illuminated. The monkey was required to move quickly from the first to the second touch pad. Then, when the monkey contacted the second touch pad, a third LED over another touch pad was illuminated and the monkey was required to move to the third touch pad. Thus, the specific sequence of movements that the monkey performed during each trial of the TRACK task was externally cued.

3.1.1. Movement related activity in the dentate and globus pallidus

In the dentate nucleus, we sampled 172 neurons that displayed task-related activity [111]. Most task-related neurons were found in the middle third of the dentate rostro-caudally. Approximately 60% of the task-related neurons (102/72) were classified as task-independent. These neurons displayed comparable patterns of movement-related activity during the REM and TRACK tasks. The majority of the task-independent neurons were located in a dorsal region of the dentate nucleus. This region is likely to be within the output channel that projects to M1 (Fig. 2).

In contrast, 40% of the task-related neurons in the dentate (70/172) were considered task-dependent. More than 75% of these neurons (54/70) were termed TRACK neurons because they displayed exclusive or enhanced ($> \pm 50\%$) changes in activity during the TRACK task compared to the REM task. Many TRACK neurons were located ventral and lateral to dentate neurons that were task-independent. This localization suggests that TRACK neurons are within the output channel that innervates the PMv (see Fig. 2). Thus, the neurons in this output channel appear to be preferentially involved in the generation and control of sequential movements that are visually guided.

In the basal ganglia, we recorded 230 pallidal neurons that displayed a significant change in activity during the performance of the REM and/or TRACK task [112]. Most of these neurons were found in approximately the middle third of the globus pallidus, rostro-caudally. Two-thirds of these pallidal neurons were considered task-dependent because they displayed exclusive or enhanced ($> 50\%$) changes in activity for one of the tasks. Approximately 65% of the task-dependent neurons displayed exclusive or enhanced changes in activity for the REM task (REM neurons). Interestingly, many of the REM neurons were located dorsal and medial to GP neurons that were task-independent (Fig. 5). The pallidal region containing REM neurons is potentially within the output channel that innervates the SMA (Figs. 3 and 5). Thus, this output channel may be specifically involved in the guidance of sequential movements based on internal cues.

Another group of pallidal neurons displayed preferential changes in activity during the TRACK task (TRACK neurons, not illustrated) [112]. These neurons were found more ventrally in GPi, potentially in the output channel that innervates the PMv (see Fig. 3). Consequently, this output channel may be particularly concerned with guiding movement based on external cues.

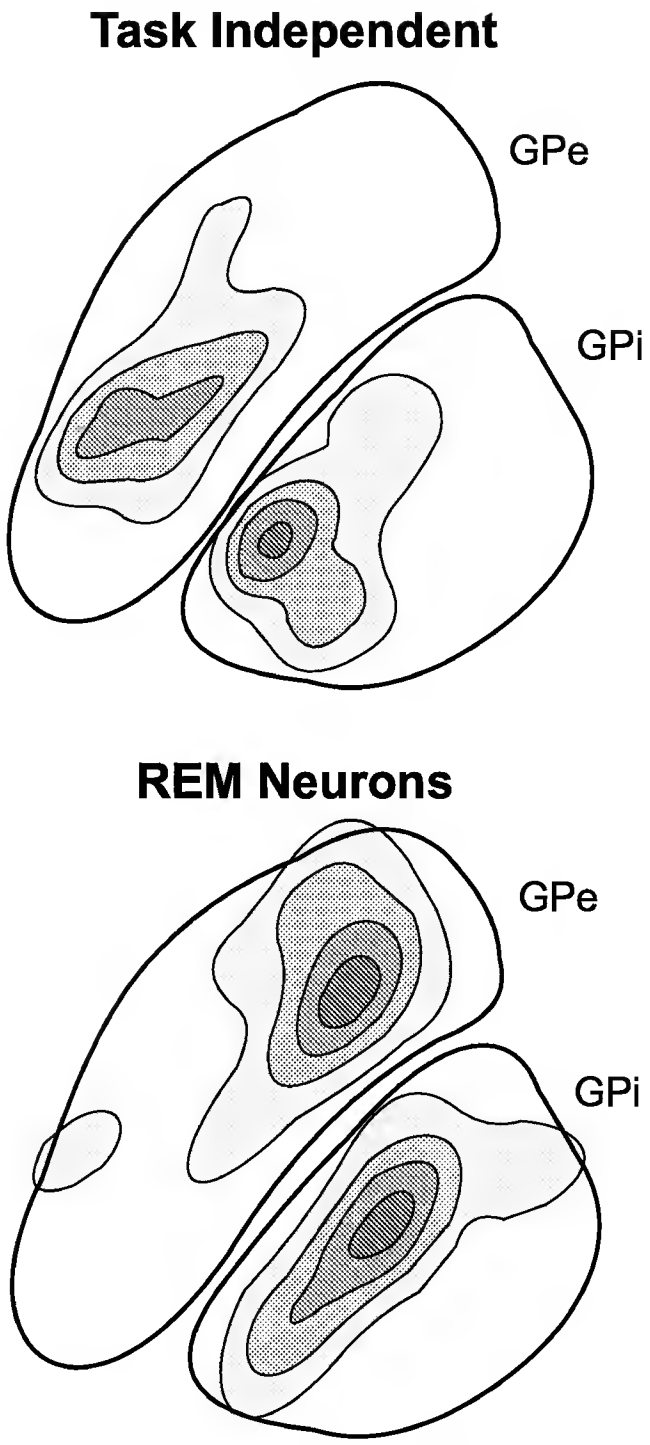

Fig. 5. Distribution of movement related neurons in the globus pallidus. The relative density of task related neurons in the two pallidal segments is indicated by shading (darker shading indicates greater density). Task independent neurons displayed comparable changes in activity during the REM and TRACK tasks. REM neurons displayed exclusive or enhanced ($> 50\%$) changes in activity during the REM task (see text for details). Note the tendency for REM neurons to be in pallidal regions that were dorsal to task independent neurons. Adapted from [151].

3.1.2. Instruction related activity in the dentate and globus pallidus

Approximately 15% of the task-related neurons in both the dentate and globus pallidus were 'instruction-related' (I-related), that is, they displayed changes in activity during the instructed delay period of the REM task (e.g., Fig. 6) [113]. Some of these I-related neurons displayed transient changes in activity immediately after the presentation of visual cues (Fig. 6, 'Cue' neuron). Other I-related neurons displayed changes in activity only during the delay period following the illumination of the 3 instruction LEDs (Fig. 6, 'Delay' neuron). Some of these Delay neurons displayed activity that was specific for the particular remembered sequence of movements that the animal was preparing to perform. Still other I-related neurons displayed changes in activity during both task periods (Fig. 6, 'Cue + Delay' neuron).

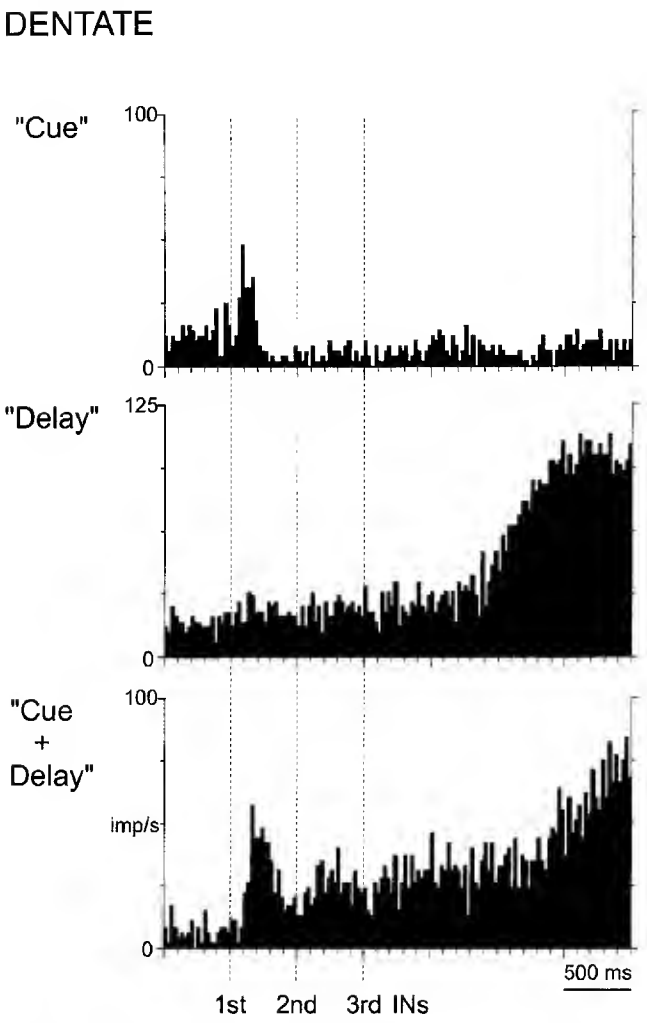

Fig. 6. Responses of I-Related neurons in the dentate. The rasters and averages illustrate the activity of three different types of I-related neurons during the instructed delay period of the REM task (1st, 2nd and 3rd INs). The trials are aligned on the presentation of the third instruction. The bin width for the averages is 20 msec. The trials illustrated all began with the illumination of LED #4. Adapted from [113].

The I-related activity in the globus pallidus and dentate is very similar to the activity found in prefrontal cortex during instructed delay periods [45–49,83,84,115,170]. In fact, one study of prefrontal cortex found instruction-related activity during a sequential movement task very similar to the one used in our analysis of GPi and dentate activity [46]. I-related neurons tended to be located in dorsomedial regions of the globus pallidus and ventral regions of the dentate [113]. These observations suggest that I-related neurons are within output channels that innervate regions of prefrontal cortex involved in working memory (e.g., areas 46 and 9), or possibly within output channels that innervate cortical areas involved in motor preparation (e.g., the SMA and pre-SMA). Thus, pallidal and dentate activity during instructed delay periods could participate in higher order motor and/or cognitive functions.

3.2. Functional activation of human basal ganglia and cerebellar output nuclei during cognitive tasks

Few studies have examined functional activation in the output nuclei of the basal ganglia and cerebellum during motor or cognitive tasks (but see [51,74,77,78,81]). This is due, at least in part, to the small size of the GPi and dentate, and their location deep within the brain. Both of these factors present substantial technical barriers for most imaging techniques. However, several studies of functional activation within the basal ganglia or cerebellum have produced results that are relevant to this presentation.

3.2.1. Functional imaging of the dentate nucleus and related structures

Kim, Ugurbil and Strick [81] used fMRI to examine activation of the dentate nucleus associated with two behavioral tasks. In one task, termed the 'Visually Guided Task', a small pegboard with nine holes was securely positioned over each subject's chest. The board contained four red pegs in the holes at its right end. Subjects were asked to move each peg, one hole at a time, to the holes at the opposite end of the board. The second task, termed the 'Insanity Task', used the same pegboard as the Visually Guided Task. However, in this case, four red pegs were placed in holes at the right end of the board, and four blue pegs were placed in holes at the left end. Subjects were instructed to move the four pegs of each color from one end of the peg board to the other using three rules: (1) move one peg at a time; (2) move to an adjacent open space or jump an adjacent peg (of a different color); and (3) move forwards, never backwards. Subjects easily performed the Visually Guided task, but no subject solved the Insanity Task during the period of scanning. Thus, the brain activation during the Insanity Task in part reflects the subjects' attempts to solve the pegboard puzzle, as well as visually guided movements of the pegs.

All of the subjects displayed a large bilateral activation in the dentate during attempts to solve the Insanity Task. Furthermore, in every subject, the extent of this activation was 3–4 times larger than that found during the Visually Guided Task. In addition, the ventral portions of the dentate that were prominently activated by the Insanity Task differed from the portions of this nucleus activated during the Visually Guided Task. These results suggested that the regions of the dentate involved in cognitive processing are distinct from the dentate regions involved in the control of eye and limb movements. The ventral regions of the dentate that were activated during the Insanity Task potentially include output channels that innervate prefrontal regions of cortex. Portions of areas 9 and 46 have been shown to be strongly activated in human subjects who are engaged in difficult planning tasks, such as the Tower of London task [11,120]. Thus, in humans the portion of the dentate that likely projects to the prefrontal cortex appears to be involved in the same type of tasks as the cortical areas it innervates.

In a study using positron emission tomography (PET), Jueptner and colleagues [77,78] asked normal subjects to learn sequences of 8 finger movements (key presses). They then compared the brain activity during: (1) learning of new sequences; (2) performance of previously learned sequences; and (3) a 'baseline' condition. An examination of their data shows that the 'automatic' performance of previously learned sequences resulted in preferential changes in activity in the primary motor cortex, motor areas on the medial wall of the hemisphere, medial regions of cerebellar cortex and dorsal portions of the deep cerebellar nuclei [77,78]. These brain regions are thought to participate in cerebro-cerebellar circuits which interconnect motor areas of the cerebral cortex and neo-cerebellar regions. In contrast, another set of brain sites displayed preferential changes in activity during the learning of new sequences. These sites included areas 9 and 46, lateral portions of the cerebellar hemispheres, ventrolateral regions of the deep cerebellar nuclei, and caudal paralaminar portions of the mediodorsal nucleus of the thalamus. All of these brain regions are thought to be components of a cerebro-cerebellar circuit which interconnects prefrontal cortex and neo-cerebellar regions. Thus, cerebro-cerebellar loops with motor areas of cortex appear to be concerned with aspects of motor execution whereas those with prefrontal cortex appear to be more concerned with learning new movement sequences.

3.2.2. Functional imaging of the globus pallidus and related structures

A further examination of the data in the study by Jueptner and colleagues [77,78] reveals the presence of some selective changes in activity in basal ganglia-related structures during cognitive versus motor tasks in humans. Within the basal ganglia, the automatic performance of previously learned sequences was associated with increased activation in the sensorimotor portion of the putamen. In contrast, new sequence learning was associated with preferential changes in activity within the dorsolateral caudate, rostrodorsal portions of the globus pallidus and the ventral anterior nucleus of the thalamus. All of these structures are thought to be part of basal ganglia loops with areas 9 and 46 (see [2]). Thus, the performance and learning of sequential movements appear to involve activation in different basal ganglia circuits.

In another PET study, Owen and colleagues [119] examined the patterns of GPi activation in normal subjects and in patients with Parkinson's disease during the performance of 3 different tasks: (1) a difficult planning task (the Tower of London task); (2) a spatial working memory task; and (3) simple visually guided movements. The planning and spatial working memory tasks had been shown in prior studies from this group to be associated with strong activation of areas 9 and 46 in normal subjects [11,120]. In this study, the GPi displayed striking activation during the planning and spatial working memory tasks in normal subjects, but not in patients with Parkinson's disease. Moreover, patients with Parkinson's disease had previously been shown to be impaired in the performance of the planning and spatial working memory tasks [121]. These results suggest that the basal ganglia loop with prefrontal areas of cortex is involved in cognitive operations such as planning of a difficult series of actions and monitoring the spatial location of different cues.

4. Implications of anatomical and physiological results

4.1. Individual output channels and loops concerned with individual behaviors

Our anatomical observations provide evidence that the basal ganglia and cerebellum participate in multiple spatially separate loops with the cerebral cortex. Furthermore, the physiological results just presented suggest that each loop is involved in a distinct aspect of behavior. Changes in activity in an output channel parallel the changes in activity seen in the cortical area it innervates. In the final part of this review, we discuss some of the important implications of this arrangement. In particular, we would like to point out how the arrangement of output channels in the basal ganglia and cerebellum may provide a useful framework for understanding the consequences of basal ganglia and cerebellar pathology.

4.2. Lesions and disease states may produce symptoms by affecting one or more loop(s)

One prediction from our results is that a lesion or disturbance of a particular subcortical loop should produce a behavioral disturbance that resembles the disturbance seen after damage to the cortical area subserved by that

loop. Space does not permit us to review all of the studies of basal ganglia and cerebellar damage that might support this prediction. However, in the remainder of this presentation we will provide a few striking examples of the unique consequences of dysfunction in selected loops.

4.2.1. Cerebellar dysfunction

There is now considerable evidence that gross cerebellar damage can lead to the development of certain cognitive and perceptual difficulties, as well as motor symptoms (reviewed in [1,17,42,53,71,87–91,110,125,137–140]). Given our anatomical and physiological results, one might predict that damage to the ventral portion of the dentate, or the regions of cerebellar cortex that innervate it, would result in cognitive deficits resembling those seen after lesions of areas 9 or 46. Some support for this conclusion comes from several recent studies of humans with cerebellar lesions. Fiez and colleagues reported a patient, designated RC1, with damage to the lateral portion of his right cerebellar cortex [42]. This patient exhibited few classical signs of cerebellar damage, but was impaired on the performance of specific types of rule-based memory tasks. In fact, the deficits appeared on cognitive tasks that activate lateral portions of the cerebellar hemispheres, as well as area 9 and 46 during imaging studies of normal subjects [43,127,128]. Furthermore, the results of a recent anatomical study suggest that the lateral region of cerebellar cortex that was activated in cognitive tasks and damaged in RC1 is part of the cerebellar loop with prefrontal cortex (Kelly and Strick, unpublished observations).

4.2.2. Basal ganglia dysfunction

It has also long been recognized that damage to basal ganglia circuitry produces cognitive as well as motor symptoms [2,23,30,35–37,41,72,73,85,86,92,106,121,122, 124,125,131,133,141,142,153,171]. For example, Parkinson's disease begins with pathological changes that are predominately in sensorimotor portions of the striatum (e.g., mid putamen; see [82]) and is associated at its onset with largely motor symptoms (although recent studies also indicate some higher order deficits are present early in the course of the disease [35,37,41,73,92,118,158]). In contrast, Huntington's disease begins with pathological changes primarily in the associative portions of the striatum (e.g., anterior caudate; see [164]) and is associated at its onset with primarily cognitive disturbances (reviewed in [23,60,72,86]). The sensorimotor and associative regions of the striatum provide input to different portions of the output nuclei of the basal ganglia (see [2]). Thus, differences in the initial symptoms of Parkinson's and Huntington's disease could be a reflection of abnormal activity in output channels to different cortical areas.

Primates given chronic high doses of the selective neurotoxin MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) develop all of the motor symptoms of Parkinson's disease, and even display neuropathological changes that are almost identical to the idiopathic syndrome. Interestingly, chronic low dose treatment of primates with MPTP produces profound cognitive and visual deficits prior to the development of gross motor impairments (see [131,141, 142]). The absence of motor impairments and the presence of cognitive changes suggest that the major effects of low dose MPTP treatment occur in the caudate and not the putamen. A detailed examination of the pathology following low dose treatment could provide a critical test of the segregated loop hypothesis.

Parkinson's disease and MPTP damage the input side of basal ganglia processing (the caudate/putamen). There is also growing evidence that pathology within the output nuclei of the basal ganglia results in cognitive and sensory dysfunction, as well as motor dysfunction [2,30,85,153]. For example, an analysis of the effects of ventral pallidotomy for the treatment of Parkinson's disease by Trepanier and colleagues [160] concluded that even this refined surgical procedure can cause cognitive impairments that are similar to some of the effects of prefrontal damage. Our anatomical results provide a simple explanation for these cognitive deficits. Surgical lesions of the globus pallidus are intended to interrupt abnormal signals in motor circuits through the basal ganglia by selective destruction of output channels in GPi that innervate motor areas of the cerebral cortex. However, to be effective these lesions must be large. Pallidal output channels that innervate the prefrontal cortex are located adjacent to those that innervate motor areas. Thus, it is likely that the cognitive deficits result from interrupting output channels that innervate prefrontal, as well as motor areas of cortex.

There is also evidence that lesions of SNpr produce prominent alterations in non-motor behavior. Perhaps the best example is a report of a patient with a bilateral stroke involving the SNpr [97]. The patient demonstrated profound deficits in working memory, visual hallucinations, and mild neurological symptoms, including oculomotor abnormalities. The SNpr contains output channels directed at oculomotor, prefrontal and inferotemporal areas of cerebral cortex (Figs. 3 and 4). All of these output channels are packed into a relatively small area. The working memory deficits in this patient could be a consequence of damage to nigral output channels to prefrontal cortex, while the oculomotor deficits could be the result of damage to the output channel that targets the FEF. We have previously argued that alterations in the nigral output channel to inferotemporal cortex can cause visual hallucinations [99]. Thus, the anatomical arrangement of output channels in SNpr and the cortical areas they innervate provides a plausible explanation for the remarkably diverse set of symptoms that can arise from nigral damage.

During the course of deep brain stimulation for Parkinson's disease, Bejjani and colleagues [14] reported that stimulation within the SNpr produced a change in facial expression, followed by a major depressive episode. These alterations were highly replicable and disappeared less

than 90 s after stimulation was terminated. Some nigral output channels are thought to target cortical areas concerned with the regulation of emotion (e.g., anterior cingulate/medial orbitofrontal cortices, temporal pole) [2]. Thus, the behavioral changes evoked by stimulation may have been due to abnormal activation of these output channels. This possibility merits further investigation because of the insights it might provide into potential treatments for intractable depression.

4.2.3. Possible relevance for schizophrenia and other psychiatric disorders

We are struck by the apparent similarity between the symptoms displayed by the two patients with nigral lesions just discussed and the type of symptoms most often reported in patients with schizophrenia. Unmedicated, first-episode schizophrenics frequently display 'soft' neurological signs, including deficits in smooth pursuit eye movements and saccadic dysmetria. In addition, they display affective disturbances (emotional blunting), cognitive deficits and or altered perceptions (including hallucinations) (see [67,68,123,147]). We have evidence that shows how each of these symptoms can be produced by alterations of a single subcortical site, the SNpr. Thus, we wonder whether the oculomotor, emotional, cognitive and perceptual disturbances reported in schizophrenia could be a direct result of abnormal nigral output to oculomotor, cingulate/orbitofrontal, dorsolateral prefrontal, and temporal areas of cortex. Dysfunction of other subcortical sites, such as regions of the cerebellum, could also contribute to the symptoms of schizophrenia in much the same manner that we propose for the SNpr. However, the output of the cerebellum appears to be somewhat more restricted in terms of the cortical areas it targets than the basal ganglia. For example, cerebellar output does not target inferotemporal cortex. It is also worth noting that some patients with pallidal lesions display neuropsychiatric symptoms such as cognitive deficits, obsessive-compulsive behaviors and 'psychic akinesia' [16,30,85,153]. These symptoms may result in dysfunction of pallidal output channels to prefrontal, orbitofrontal and cingulate areas of cortex (see [2,30]). Still, the SNpr may be unique in its ability to influence almost the entire range of behaviors that are disturbed in schizophrenia.

Finally, there is growing evidence that alterations in basal ganglia and cerebellar loops with non-motor areas of cortex are present in schizophrenia and other neuropsychiatric disorders including Tourette's syndrome, autism, attention deficit disorder, anxiety disorders and mood disorders (e.g., [5,7–9,12,13,15,18,21,22,24–30,34,36,38,39,44,50,56–59,64,70,75,76,79,93,95–97,109,114,130,143–149,154–156,161,163,166,167,172,173,175]). Further experiments are needed to determine the number and arrangement of basal ganglia and cerebellar loops with the cerebral cortex. We believe that defining the functional organization of these circuits will lead to important insights into the role of the basal ganglia and cerebellum in normal and abnormal behavior.

5. Summary and conclusions

Recent anatomical studies have challenged the view that basal ganglia and cerebellum are solely concerned with motor control. It is now apparent that multiple cortical areas are the target of basal ganglia and cerebellar output, including not only the primary motor cortex, but also subdivisions of premotor, oculomotor, prefrontal and infer-

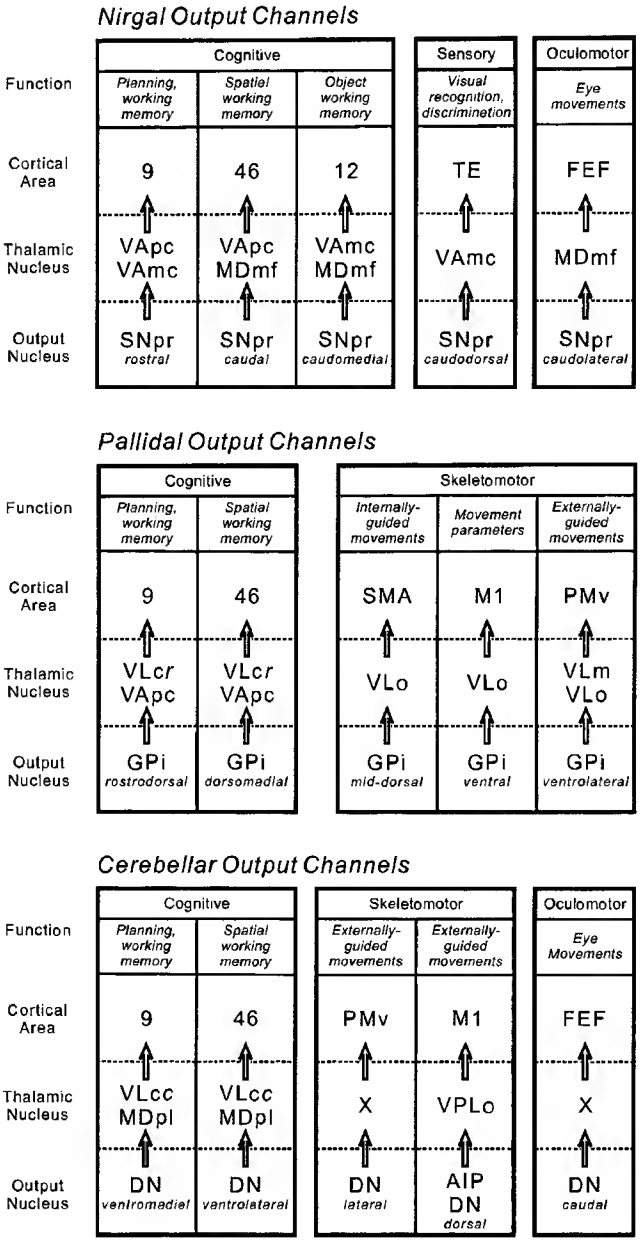

Fig. 7. Motor and non-motor output channels. The basal ganglia and cerebellum project to a diverse set of cortical areas via the thalamus. These projections form anatomically and functionally distinct output channels. AIP, anterior interpositus nucleus. Thalamic abbreviations according to Olszewski [116].

otemporal areas of cortex. The output to individual cortical areas appears to originate from distinct clusters of neurons in the GPi, SNpr and dentate that are termed output channels (Fig. 7). Each output channel projects to a distinct area of cerebral cortex via the thalamus. Physiological recordings in awake trained primates and functional imaging studies in humans suggest that individual output channels are involved in different functions which resemble those of the cortical area they innervate. Clinical studies suggest that dysfunction in individual basal ganglia or cerebellar loops with the cerebral cortex may underlie the development of specific neurological and psychiatric symptoms. Future studies are needed to determine the full extent of the cerebral cortex that is influenced by basal ganglia and cerebellar output, and the functional significance of this influence.

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